## REMARKS

The Office Action dated August 27, 2002, has been received and reviewed. Claims 1-10 and 13 are currently pending in this application. Claims 2 and 8 have been cancelled without prejudice or disclaimer in the present response, as these claims were restricted in the Office Action as being drawn to a non-elected invention. Claims 1, 3 and 13 have been amended to remove the phrase "in need thereof". Applicants note that none of these amendments are narrowing in effect. The marked-up version of the claim amendments is appended hereto and is captioned "Version with Markings to Show Changes Made." The amendments to the specification and the outstanding rejections are addressed below. Applicants respectfully request reconsideration of the application as amended herein and in view of the arguments below.

### I. Claim Amendments

Applicants have cancelled claims 2 and 8 without prejudice or disclaimer. Claims 1, 3 and 13 have been amended to remove the phrase "in need thereof" as suggested by the Examiner. Support for the changes and new claims may be found throughout the application. It is respectfully submitted that the claims as amended are stated in a manner that is not narrower than the original claims.

### II. Rejections Under 35 U.S.C. §112, First Paragraph

Claims 1, 3-7, 9-10 and 13 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention and as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse this rejection.

First, Applicants note that originally presented claims are strongly presumed to satisfy the written description requirement. Contrary to the argument presented in the Official Action, Applicants are not attempting to preempt the future before it has arrived, but rather are patenting a new use of a generic category of materials, numerous embodiments of which have already arrived. The patenting of new uses has long been considered appropriate subject

matter for patenting, as exemplified by the numerous issued United States patents directed to such new uses.

Applicants note that the "test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." (MPEP §2164.01, citing *In re Wands*, 858 F.2d 731, 737). Furthermore, the test for whether or not the enablement requirement has been met involves determining whether or not practice of the invention as claimed involves "undue experimentation". It has long been settled that "the key word is 'undue', not 'experimentation'". *In re Angstadt*, 190 USPQ 214, 219 (C.C.P.A. 1976). In the present case, the references cited by the Examiner in the previous Office Action, taken together with the references cited by the Applicants in this reply show only that the application of the current technology requires routine effort, and not undue experimentation.

Applicants submit that the present application contains an adequate written description. One of skill in the art would readily be able to envision the scope of the invention as presently claimed. Applicants submit that as stated in the specification on pages 4-5, multiple studies have shown that in normal adult tissues, telomere length and telomerase activity appear to correlate well with the differentiation stage of a cell, as well as its potential to act as a stem cell upon appropriate stimulation (Greider (1998) *Current Biol.* 8:R178-R181; Lavker, et al. (1993) *J. Invest. Dermatol.* (Suppl.) 101:16S-26S; Mason et al. (1997) *Am. J. Respir. Cell Mol. Biol.* 16:355-363). Telomerase expression correlates with self-renewal potential in many cell types, including epithelial cells (Morrison, et al. (1997) *Cell* 86:287-298; Yasumoto et al. (1996) *Oncogene* 13:433-439). Unlike tumor cells, stem cells are not immortal, and show decreasing telomere length with increasing age (Morrison, et al. (1996) *Nature Med.* 2:202-206; Vaziri, et al. (1994) *Proc. Nat. Acad. Sci. USA* 91:9857-9860). Thus, telomerase may regulate self-renewal capacity by reducing the rate at which telomeres shorten. Therefore, one of skill in the art can lean upon the action of telomerase to study stem cell lines.

Example 2 contained in the specification of the present invention discloses:

> *Telomerase expression is restricted to a subpopulation of mouse lung epithelial cells through embryonic development, and is down regulated following birth.* Lung sections from staged mouse embryos were fixed, paraffin embedded and sectioned, then immunostained using an antibody raised against the catalytic subunit of human telomerase, hTERT, which cross-reacts with both mouse and rat TERT. Whole lungs were obtained from embryos at gestational age E18 (**Figure 8**, E 18), and from neonates

at one hour post-birth (D 0), and at two days (D 2), four days (D 4), six days (D 6), and nine days (D 9) following birth. Scattered epithelial and mesenchymal staining in lungs of mouse embryos from gestational age E18 through post birth day 6 was found. Epithelial expression appeared strongest at E18 through the day of birth, with staining confined to individual cells. Expression appeared to peak at this time, then declined over the next nine days. During this period, the generalized expression pattern became restricted to discrete patches near the external surface of the lung (**Figure 8**, D 6). By day nine, telomerase expression was almost undetectable. A similar lack of mTERT expression was observed by immunostaining adult mouse lung epithelium (data not shown).

*Telomerase expression in adult lung is induced during the repair phase following hyperoxic injury.* Previous studies showed that exposure of animals to hyperoxia induces a proliferative response in normally quiescent lung tissue as part of a process of repair. In order to determine if re-induction of telomerase expression was a part of this process, fixed, paraffin-embedded sections were obtained from the lungs of adult rats treated with hyperoxia for 48 hours, then allowed to recover in room air for various periods of time. Lung sections from age- and weight-matched animals, which breathed room air throughout the treatment and recovery period, were used as controls. Sections were immunostained as described for embryonic and neonatal mouse lung sections, using the same anti-TERT antibody. Analysis showed that, as with adult mice, negligible TERT expression could be detected in control adult rat lung epithelium (**Figure 9**, top panel). In contrast, TERT expression increased dramatically in the lung tissue of animals subjected to hyperoxia for 48 hours, then allowed to recover in room air for 48 hours (**Figure 9**, bottom panel). While scattered TERT expression was observed at 0 and 120 hours recovery following 48 hours of hyperoxia treatment (data not shown), peak telomerase expression occurred during the period 48 hours following treatment.

The data presented herein demonstrate that telomerase, the polymerase responsible for telomere maintenance and extended cellular life span, is expressed in developing rodent lung, then down-regulated after birth. The *in situ* results observed here demonstrate that the percentage of cells which express telomerase is higher in the repairing adult lung than the percentage observed in developing lung tissue, though the percentages of positive cells in the isolated, AEC enriched populations in culture is similar. The large numbers of telomerase-positive cells in the AEC population isolated from repairing lung could represent those cells which have repopulated the damaged tissue during the injury and recovery periods, and which may soon exit the proliferative pool in order to take up AEC2 differentiated functions. Therefore, based upon these results and the knowledge of telomerase activity, one of skill in

the art can lean upon the action of telomerase to study stem cell lines as disclosed in the present application.

Work from the hepatology field now strongly supports the concept that both endogenous and exogenous stem cells contribute to the regeneration of this organ in response to injury. Moreover, numerous papers now appearing attest to the general and reversible plasticity of stem cells both from bone marrow, fat and other tissues such as lung. Recent studies have shown that tissue specific stem cells can differentiate into lineages other than the tissue of origin. Studies have demonstrated that after transplantation of bone marrow or enriched haematopoietic stem cells, lung cells of donor origin have been detected. See, e.g., Jiang et al., *Nature,* 418:41-49 (2002) (**Exhibit A**); Krause et al., *Cell*, 105:369-377 (2001); Kotton et al., *Development,* 128:5181-5188 (2001) (**Exhibit B**); and Krause et al., *Gene Ther.,* 9:754-758 (2002). Therefore, any number of representative stem or progenitor cells may be used to regenerate the lung alveolar surface in a mammal. Additionally, further studies have illustrates that lung injury per se enhances the uptake of stem cells into lung and their participation in lung repair (Theise et al., *Exp. Hematol.,* 30:1333-1338 (2002) (**Exhibit C**). Applicants further submit that current studies demonstrate that populations of stem cells already resident in lung are able to repopulate bone marrow. Asakura et al., *Exp. Hematol.,* 30:1339-1345 (2002) (**Exhibit D**). Thus, the presence of stem cells in the lung has been demonstrated. Additionally, unique populations of resident stem cells are now well identified within the peripheral lung. Giangreco et al., *Am. J. Pathol.,* 161:173-82 (2002) (**Exhibit E**). Therefore, Applicants submit that stem cells that take up residence in the lung have been isolated from bone marrow samples and transplanted into animals and humans, thus, illustrating that the present application is enabled. Applicants further note that many different kinds of stem cells from various sources in the body can take up residence in the lung and contribute to lung injury repair and regeneration.

Resident lung or other circulating stem cells can repair the gas diffusion capacity of the peripheral alveolar parts of the lung. This is borne out by the findings of Jiang et al. (2002) and Kotton et al. (2002), as well as by Theise et al. (2002). Additional evidence supporting that alveolar epithelial cells can be repaired by stem cells comes from the findings of Ali et al. who reported that alveolar epithelial cells can be derived directly from murine embryonic stem cells in culture. *Tissue Eng.,* 8:541-550 (2002). Thus, the lung is the organ most efficiently engrafted by exogenous stem cells (up to 20% of alveolar surface in resting lung) as compared to less than 10% in other organs as shown both by Jiang et al.

(2002) and in the present application. This is most likely due to extensive trapping of circulating stem cells in the peripheral alveolar lung circulation, which is very narrow and thus strains out stein cells from the entire cardiac output. Watanabe et al., *Cytotherapy*, 3:461-6 (2001). Accordingly, the present application is enabled.

Applicants submit that later publications may be evidence of the state of art existing on the filing date of the application. See, *In re Hogan,* 559 F.2d 595, 605- 07, 194 U.S.P.Q. 527, 536-38 (CCPA 1977); *In re Fisher*, 427 F.2d 833, 839, 166 U.S.P.Q. 18, 24 (CCPA 1970). In *Fisher,* the Court set forth the basic considerations respecting enablement and the potential for domination of future developments, describing the effect of predictability factors upon those considerations. *Id.* Applicants submit that the results as shown in the above and previously referenced articles, and in the present application, support the claims of the present application. One of skill in the art knows that exogenous stem cells can home to the lung and initiate alveolar surface repair and are readily obtained from peripheral blood, cord blood or bone marrow. Simple intravenous infusion of these cell populations is sufficient to get significant uptake into the alveolar regions of the lung and these stem cells will then contribute to repair and regeneration of the alveolar epithelium. Furthermore, resident stem cells have been proven to exist in the lung that not only can contribute to lung repair and regeneration but that can also regenerate other tissues as well. Therefore, Applicants submit that one of skill in the art could follow the steps of the claims of the present application.

Furthermore, Applicants submit that with the common knowledge of overcoming the issues of graft versus host disease one could readily transplant a lung as recited in the present claims. In the Official Action, it is admitted that "the state of the art for lung transplantation has gained widespread acceptance as a therapeutic option for a diverse array of lung diseases". Problems with the technique are noted, but it is noted that most beneficial techniques have some risks and potential side effects. There are numerous examples in the art of how to combat graft versus host disease. See, for example, U.S. Patent No. 6,368,636, wherein a method of inducing a reduced immune response against a host by foreign tissue, i.e., graft versus host disease, was alleviated by treatment with mesenchymal stem cells. Therefore, in the instant case, the state of the art is such that the USPTO can not properly shift the burden of establishing enablement to the applicant, and no reason to doubt the objective enablement provided by the specification is established (MPEP2164.04). Hence, it is respectfully submitted that this rejection should be withdrawn.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. § 112, first paragraph rejections to claims 1, 3-7, 9-10 and 13.

**III. Rejections Under 35 U.S.C. §112, Second Paragraph**

Claims 1, 3 and 13 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly the phrase "in need thereof" with respect to lungs and recipients is indefinite. Although, it is respectfully submitted that this phrase, or language substantially similar thereto, is well established language in numerous claims of issued United States patents and used simply to add context to the claims, Applicants have stricken the phrase "in need thereof" as suggested by the Examiner. Accordingly, Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. §112, second paragraph rejection to Claims 1, 3 and 13.

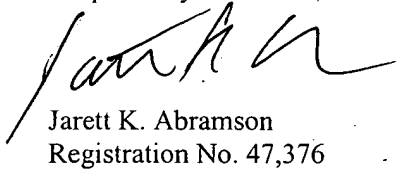
**ENTRY OF AMENDMENTS**

The amendments to the claims above should be entered by the Examiner because the amendments are supported by the as-filed specification and drawings and do not add any new matter to the application. Further, the amendments do not raise new issues or require a further search.

**CONCLUSION**

In view of the amendments and remarks presented herein, Applicants respectfully submit that the claims in the instant application define patentable subject matter. If questions should remain after consideration of the foregoing, the Examiner is kindly requested to contact Applicants' attorney at the address or telephone number given herein.

Respectfully submitted,



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Enclosures: Version With Markings to Show Changes Made
Exhibits A-E

**CERTIFICATE OF MAILING**

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Box RCE, Commissioner for Patents, Washington, DC 20231, on December 27, 2002.

Vickie Diane Prior

Vickie Diane Prior
Date of Signature: December 27, 2002

**Version With Markings To Show Changes Made**

**In the Claims:**

Please amend the claims as follows:

1. (Twice Amended) A method of stimulating the growth of lung alveolar surface in a lung [in need thereof], comprising:

providing progenitor or stem cells capable of regenerating lung alveolar surface; and

administering said progenitor or stem cells to said lung in an amount sufficient to stimulate the growth of lung alveolar surface therein.

3. (Twice Amended) The method according to claim 1, wherein said lung is *ex vivo*, and wherein said administering step is followed by the step of:

transplanting said lung into a recipient [in need thereof].

13. (Amended) An *ex vivo* method of stimulating the growth of lung alveolar surface in a lung [in need thereof], comprising:

providing progenitor or stem cells capable of regenerating lung alveolar surface; and

administering said progenitor or stem cells to said lung *ex vivo* in an amount sufficient to stimulate the growth of lung alveolar surface therein.